DETAILED ACTION

Claims 1-3, 5, 7-31, 34-35, and 37 are pending. Applicants amended claims 1, 5, and 37. Applicants newly cancelled claims 4 and 6. Applicants previously cancelled claims 32-33 and 36. Claims 9, 11-19, and 34 are withdrawn from consideration as being drawn to non-elected subject matter. **Claims 1-3, 5, 7-8, 10, 20-31, 35, and 37 are under consideration in the instant office action.** Receipt and consideration of Applicants' arguments/remarks submitted March 19, 2009 are acknowledged. All rejections not explicitly maintained in the instant office action have been withdrawn per Applicants' claim amendments and/or persuasive arguments.

Election/Restrictions

It is noted that Applicants' claim amendments have stricken the originally elected species of NK_1 receptor antagonist from the pending claims. The species election was previously expanded to include (S)-N-[2-[3,5-bis-(trifluoromethyl)phenyl]ethyl]-4-(cyclopropylmethyl)-N-methyl-a-phenyl-1-piperazineacetamide as the elected NK_1 receptor antagonist. The species election is maintained at this time.

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Specification

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Objections

Claim 1 is objected to because of the following informalities: (1) the term "dichlorophenyl" is misspelled in claim 1, line 14, (2) a hyphen should be inserted between "1" and the following parentheses in the chemical compound name bridging lines 13-14; (3) a hyphen should be inserted between "N" and the following parentheses in the last compound recited on line 16 of claim 1; (4) a hyphen should be inserted between "yl" and "carbonyl" on line 19 of claim 1 (i.e. the third line on the second page of the current claim set). Appropriate correction is required. Applicants are kindly encouraged to thoroughly review the list of NK1 receptor antagonists recited in part (b) of claim 1 for any other errors in the nomenclature of said compounds.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5, 7-31, 34-35, and 37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement (new matter). The claim(s)

contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants' original claim 1 (see 7/7/2003 claim set) originally recited 39+ specific NK1 receptor antagonist compounds, many of which were listed as alpha-numeric designations. On September 19, 2007 Applicants amended the claims to replace the alpha-numeric designations of many of the recited NK1 receptor antagonists with chemical names and provided photocopies of excerpts from various journal articles correlating specific chemical structures with many of the alpha-numeric designations. Applicants also indicate that the other alpha-numeric designations were well-known to correspond to specific drugs. Applicants' current recited list of NK1 receptor antagonists in claim 1, part (b), currently contains four compounds that do not appear to correlate to any of the alpha-numeric designations previously contained in Applicants' claims (i.e. the 4th, 6th, 14th, and 15th compounds in the currently recited list of NK1 receptor antagonists in claim 1, part (b)). Thus, this constitutes new matter. If Applicants do not believe this is new matter, Applicants are kindly requested to provide a table correlating each specific alpha-numeric designation originally recited in Applicants' claims with its corresponding chemical structure.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Applicant Claims
2. Determining the scope and contents of the prior art.
3. Ascertaining the differences between the prior art and the claims at issue, and resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 5, 7-10, 20-26, 28-31, 35, and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meissner et al. (US 2002/0115680) in view of Schnorrenberg et al. (U.S. Patent No. 6,124,296), as evidenced by "What is COPD?" (www.nhlbi.nih.gov/health/dci/Diseases/Copd/Copd_WhatIs.html - accessed on September 11, 2009).

Applicants Claim

Applicants claim (A) a pharmaceutical composition comprising (i) one or more anticholinergics of formula 1, including a solvate or hydrate thereof and (ii) one or more NK1 receptor antagonist, including a solvate or hydrate thereof and (B) a method of treatment of

chronic obstructive pulmonary diseases (COPD) comprising administering (i) and (ii) separately or together in a pharmaceutical formulation to a patient in need thereof.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Meissner teaches **the administration of anticholinergic compounds of formula I, to treat chronic obstructive pulmonary disease (COPD)** (title; abstract; [0004], [0172]; [0184]; [0188]; and claim 7). **Applicants' specific anticholinergic of formula 1 is disclosed explicitly by Meissner as a compound of particular importance ([0049] and [0051])**. Meissner discloses the synthesis of Applicants' anticholinergic compound of formula 1 in Example 1([0103]-[[0108]). Meissner discloses that pharmaceutical formulations of the invented anticholinergic compounds may be in the form of solutions [0184] and the solutions are prepared in the usual way with the addition of isotonic agents (e.g. NaCl), preservatives (e.g. p-hydroxybenzoates), stabilizers (e.g. alkali salts of EDTA), diluent (e.g. water), and organic solvents [0186]. An exemplified **aqueous propellant-free formulation is disclosed in Example C and comprises active substance (i.e. Meissner's invented anticholinergic compounds), sodium chloride (i.e. an isotonic agent), and water (i.e. a diluent**) (between paragraphs [0193]-[0194]). The active substance is prepared by dissolution in water, optionally adjusting the pH to a value of 5.5 to 6.5, and addition of sodium chloride [0194]. Example E discloses an **aqueous formulation with a pH of 3.4 comprising active substance (333.3 mg), formoterol fumarate (333.3 mg), benzalkonium chloride (10.0 mg), EDTA (50.0 mg), 1N HCl (added in an amount sufficient to result in a pH of 3.4)** [0195]-[0196]. In general, suitable amounts of Meissner's invented anticholinergic compounds are in the range of **0.05-**

90% w/w [0184] or in an amount from 1-1,000 mg [0189]. The invented anticholinergic compounds **are characterized by high efficacy even in the microgram amount** [0189]. Syrups or elixirs (i.e. liquid formulations) comprising the active substances may additionally contain sweeteners (e.g. saccharine, glycerol, or sugar) and **flavorings** (e.g. vanilla orange extract) [0185]. The compositions may also contain **suspension adjuvants, wetting agents, and preservatives** [0185].

Schnorrenberg teaches **a preference for the (S)-enantiomer of the first NK1-receptor antagonist recited in Applicants' claim 1** (Schnorrenberg's claims 1, 2, 10, and 21). Schnorrenberg's claims 12-13 teach that N-[2-[3,5-bis-(trifluoromethyl)phenyl]ethyl]-4-(cyclopropylmethyl)-N-methyl-a-phenyl-1-piperazineacetamide is **suitable for the treatment of allergic diseases of the respiratory tract (claim 12), specifically emphysema, asthma, and chronic bronchitis** (claim 13). Schnorrenberg exemplifies N-[2-[3,5-bis-(trifluoromethyl)phenyl]ethyl]-4-(cyclopropylmethyl)-N-methyl-a-phenyl-1-piperazineacetamide in Example 66 (col. 31, lines 1-15). The general synthesis of the NK1 antagonists taught by Schnorrenberg is taught (col. 11, line 1 through col. 12, line 24).

The online NIH document entitled, "What is COPD?" teaches that **the term COPD as used in the United States includes two main conditions- emphysema and chronic obstructive bronchitis** (see second page of document, first full sentence).

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Meissner lacks the teaching of compositions comprising NK1 receptor antagonists and the administration of said compounds to treat COPD. This deficiency is cured by the teachings of Schnorrenberg.

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been prima facie obvious to modify Meissner's compositions to comprise one or more neurokinin 1 (NK1) receptor antagonist (Schnorrenberg), because neurokinin receptor antagonists are known and are indicated for the treatment of COPD (Schnorrenberg). An ordinary skilled artisan would have been motivated to combine the prior art teachings because Meissner's anticholinergic compounds are indicated for the treatment of COPD and neurokinin antagonists, such as, Schnorrenberg's neurokinin 1 antagonists, are indicated for the treatment of COPD as well. It is generally considered *prima facie* obvious to combine two compounds each of which is taught by the prior art to be useful for the same purpose, in order to form a composition which is to be used for the very same purpose. The idea for combining them flows logically from their having been used individually in the prior art. See *In re Kerkhoven*, 626, F.2d 848, 205 USPQ 1069 (CCPA 1980). An ordinary skilled artisan would have had a reasonable expectation of successfully combining the prior art compositions to obtain formulations suitable for the treatment of COPD, because Meissner's invented anticholinergic compounds are indicated for the treatment of COPD and neurokinin antagonists, such as Schnorrenberg's invented neurokinin antagonists are indicated for the treatment of COPD.

Regarding the amounts of the anticholinergic compounds of Applicants' formula 1 and the NK1 receptor antagonists, the amount of a specific ingredient in a composition is clearly a

result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal amount of each ingredient needed to achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed parameters, the optimization of ingredient amounts would have been obvious at the time of applicant's invention. It is noted that Applicants' specification contains no data or other objective evidence regarding the properties of the claimed compositions and associated methods of treating COPD. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Response to Arguments

Applicant's arguments with respect to claims 1-3, 5, 7-10, 20-26, 28-31, 35, and 37 have been considered but are moot in view of the new ground(s) of rejection.

Claim 27 is rejected under 35 U.S.C. 103(a) as being unpatentable over Meissner et al. (US 2002/0115680) in view of Schnorrenberg et al. (U.S. Patent No. 6,124,296), as evidenced by "What is COPD?" (www.nhlbi.nih.gov/health/dci/Diseases/Copd/Copd_WhatIs.html - accessed on September 11, 2009) as applied to claims 1-3, 5, 7-10, 20-26, 28-31, 35, and 37 above, and further in view of Freund et al. (US 2001/0008632).

Applicants Claim

Applicants claim a pharmaceutical composition, as described above, further comprising an antioxidant selected from ascorbic acid, Vitamin A, Vitamin E, or tocopherols.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Meissner, Schnorrenberg, and "What is COPD?" are set forth above.

Freund teaches aqueous propellant-free pharmaceutical solutions comprising **any substance suitable for the treatment of respiratory diseases by inhalation administration** (title; abstract; [0001]; [0007]), such as betamimetics, **anticholinergics,** antiallergics, etc. Usually pharmaceuticals intended for inhalation are dissolved in **an aqueous or ethanolic solution**, according to the solution characteristics of the active substance [0004]. Other suitable solvents for inclusion in the formulations include **isopropyl alcohol, polyethylene glycol, glycerol**, etc. [0005]. The compositions comprise complexing agents, such as EDTA, disodium EDTA, citric acid, ascorbic acid, and nitriloacetic acid [0011]. The compositions **may also comprise additional adjuvants, such as preservatives (e.g. benzalkonium chloride)** [0010].

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Meissner lacks the teaching of compositions comprising an antioxidant, such as, ascorbic acid. This deficiency is cured by the teachings of Freund.

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been prima facie obvious to modify Meissner's compositions to comprise ascorbic acid in lieu of or in addition to EDTA, because ascorbic acid is a well-known complexing agent (Freund) and Meissner teaches that the invented compositions may comprise complexing agents, such as EDTA. An ordinary skilled artisan would have been motivated to add ascorbic acid to Meissner's invented compositions and would have had a reasonable expectation of successfully obtaining suitable formulations, because ascorbic acid is a well-known complexing agent and would reasonably be expected to function as a complexing agent alone or in combination with other complexing agents, such as EDTA. It is generally considered *prima facie* obvious to combine two compounds each of which is taught by the prior art to be useful for the same purpose (e.g. complexing agents), to form a composition which is to be used for the very same purpose. The idea for combining them flows logically from their having been used individually in the prior art. See *In re Kerkhoven*, 626, F.2d 848, 205 USPQ 1069 (CCPA 1980). Regarding the recitation in Applicants' claim that ascorbic acid is an antioxidant, this is merely an intended use of ascorbic acid, as well as a property of ascorbic acid. A compound and its properties are inseparable. Thus, the prior art is suggestive of compositions comprising ascorbic acid. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Response to Arguments

Applicant's arguments with respect to claim 27 have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

The art made of record and not relied upon is considered pertinent to applicant's disclosure. Pairet et al. (WO 2004/004724) is not prior art, but is relevant because it claims/discloses substantially similar compositions as are claimed in the instant application.

Claims 1-3, 5, 7-8, 10, 20-31, 35, and 37 are rejected. Claims 9, 11-19, and 34 are withdrawn from consideration. Claim 1 is objected. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James H. Alstrum-Acevedo whose telephone number is (571) 272-5548. The examiner is on a flexible schedule, but can normally be reached on M-F ~10am~5:30 pm, and Saturdays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on (571) 272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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